DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
250 Marquette Ave, Ste. 600 Minneapolis, MN 55401 (612)334-4100 Fax:(612)334-4134	4/10/2019-4/26/2019* FEI NUMBER 3015212514

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
[redacted] Clinical Investigator

FIRM NAME	STREET ADDRESS
[redacted]	Hennepin County Medical Center, Dept Of Emergency Medicine, 701 Park Ave
CITY, STATE, ZIP CODE, COUNTRY Minneapolis, MN 55415-1623	TYPE ESTABLISHMENT INSPECTED Sponsor-Investigator

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM I OBSERVED:

OBSERVATION 1

The sponsor failed to submit an IND to the FDA prior to conducting a clinical investigation with an investigational new drug.

Specifically, studies [redacted] were conducted without submission of Investigational New Drug (IND) applications to the FDA and do not appear to meet the IND exemption criteria, though the study was approved by the local Institutional Review Board (IRB).

OBSERVATION 2

Legally effective informed consent was not obtained from a subject or the subject's legally authorized representative, and the situation did not meet the criteria in 21 CFR 50.23 - 50.24 for exception.

Specifically, subjects were enrolled in studies [redacted] without obtaining informed consent from the subjects or their legally authorized representatives; neither study appeared to meet criteria for exception from informed consent, though the studies were approved by the local IRB.

OBSERVATION 3

An investigation was not conducted in accordance with the investigational plan.

Specifically,

a. Serious Adverse Events (SAE) were not reported in a timely fashion to the IRB as required by the Institutional Review Board (IRB) written procedures and IRB study approval letters. IRB written procedure Attachment EEE requires all serious adverse events related to the study treatment (or more likely related than unrelated), be reported within five working days of knowledge of the event.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE		DATE ISSUED
	Kellie L Thommes, Investigator	Kellie L Thommes Investigator Signed By: Kellie L. Thommes -S Date Signed: 04-26-2019 13:02:31 X	4/26/2019

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1. For study [redacted]:

   A. Subject 12 was enrolled in the study on October 17, 2014 and died in hospital on November 12, 2014: this death was not reported to the IRB as required by IRB written procedure Attachment EE, which requires the reporting of any untoward medical occurrence that results in death within 30 days if the event is not thought to be related to the study treatment. In the May 8, 2015 Annual Re-approval Continuing Review Report, SAEs are reported via an attached published manuscript. Other adverse events (hypersalivation, emergence reaction, vomiting, dystonia, laryngospasm, akathisia) were reported only via the manuscript.

   B. For study [redacted] 29 subjects were endotracheally intubated and placed on respirators following administration of the study drugs (subjects 12, 44, 66, 69, 71,74, 76, 80, 82, 83, 86, 88, 90, 93, 96, 98, 100, 101, 102, 107, 109, 114, 116, 120, 127, 137, 142, 143, and 144). No adverse events were listed on the Adverse Event log signed by [redacted]

   Nineteen of these events were reported in summary fashion in an email from [redacted] to the IRB on June 1, 2015 as "...the intubation rate for patients in the ketamine arm is significantly higher"; this summary did not meet the requirement to report such events to the IRB within five working days. The summary noted that 19 (44%) of the 43 subjects who received ketamine required intubation, and two (3%) of 64 subjects who received haloperidol required intubation. After this date, an additional 40 subjects were enrolled, and subsequent intubation events were reported only in a published manuscript on April 22, 2016. The Annual Re-approval Continuing Review Report submitted by [redacted] on May 18, 2016 stated there were no serious adverse events, but referred to the manuscript which stated that 39% of the ketamine subjects had required intubation (reflecting the additional six ketamine and one haloperidol subjects intubated).

2. For study [redacted] the first subject was enrolled on August 5, 2017, and the first intubation occurred August 14, 2017. The 51 ketamine and 10 midazolam subject intubation events were reported only in summary form on the April 24, 2018 Annual Re-approval Continuing Review Report submitted

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by [redacted] to the IRB; this document also states there were no SAEs. No adverse events are documented on the Adverse Event log signed by [redacted] on April 27, 2018.

b. All study activities required by the study plans were not done as follows:

1. For study [redacted], of the 22 files I reviewed, I found that:

   A. Research volunteers who collected study data did not have documented study training for subjects 6, 9, 11, 12, 14, 19, 20, 24, 31, 34, 69, 70, 72, 75, and 76.

   B. Source records did not indicate the presence or absence of a Legally Authorized Representative (LAR) as required by the study plan. Data collection forms for Subjects 9, 20, 21, 34, 72, and 76 did not contain this information.

   C. A stopwatch was not used to accurately capture the primary endpoint of time to sedation for Subjects 11, 16, 34, 66, and 75.

   D. Subjects 9, 10, 66, and 71 did not have documentation that they received the study information sheet informing them of their participation in the study when required.

   E. Documentation of vital signs on the study data collection form for Subjects 34 and 74 was not started until about one hour after study drug administration. The study plan requires documentation every five minutes until adequate sedation is achieved, and then every 30 minutes.

2. For study [redacted] in my review of 35 randomly selected subject files, I found:

   A. Paramedics without documented training on the study plan performed eligibility and enrollment determinations, as well as administration of the study drugs, for 30 of these study subjects.

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B. Subjects 1, 80, 124, 200,201, 204, 316, and 317 did not have documentation that they received the study information sheet informing them of their participation in the study at the designated time.

C. Study data collection forms were completed by research volunteers with no record of study plan training for Subjects 5, 78, 200, 201, 204, 207, 316, 317, and 320.

c. Deviations listed in the paragraphs above were not reported in the Annual Re-approval Continuing Review Reports as required by the IRB written procedure Attachment EEE, which requires any protocol deviation in which there is only minimal risk to the subject or others be reported on the next Annual Re-approval Continuing Review Report. No deviations were reported in the annual reports submitted by [redacted] to the IRB for either study [redacted].

OBSERVATION 4

Failure to ensure proper monitoring of the study.

Specifically, the sponsor did not ensure appropriate monitoring was performed of studies [redacted].

OBSERVATION 5

Investigational drug disposition records are not adequate with respect to dates, quantity and use by subjects.

Specifically, no clinical investigator-required investigational drug use and disposition records were maintained for studies [redacted].

OBSERVATION 6

Not all changes in research activity were approved by an Institutional Review Board prior to implementation.

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Specifically, study [redacted] was suspended and study related personnel were instructed to use the standard West Metro Advanced Life Support protocols during the approximately two week period surrounding the 2018 Super Bowl that was held in Minneapolis, MN, without approval from the IRB prior to implementation.

***DATES OF INSPECTION**
4/10/2019(Wed), 4/11/2019(Thu), 4/12/2019(Fri), 4/15/2019(Mon), 4/17/2019(Wed), 4/18/2019(Thu), 4/19/2019(Fri), 4/22/2019(Mon), 4/26/2019(Fri)

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."